

Editorial

Adrenomedullin in the treatment of pulmonary hypertension

Pulmonary hypertension is seen in patients in whom there is an increased pulmonary pressure (systolic pulmonary/systemic arterial pressure > 60%; > 15–20 mm Hg). The disease slowly progresses, applying stress on the right heart function leading to heart failure and death. Although the precise mechanism of development of precapillary pulmonary hypertension remains to be defined, understanding of the local factors that control pulmonary vascular tone and structure has increased greatly in the past decade. It is known that the endothelium releases several potent vasoactive mediators, including endothelin-1, prostacyclin, and endothelium derived relaxing factor, nitric oxide (NO). Decreased production of nitric oxide and prostacyclin, and increased release of endothelin, have been shown to promote pulmonary vasoconstriction resulting in pulmonary hypertension.¹ The vascular endothelium expresses receptors for ligands that play an important role in maintaining pulmonary vascular tone.²

Adrenomedullin: a hypotensive agent

Adrenomedullin, a peptide with a molecular weight of 6047 daltons first isolated from human pheochromocytoma cells, has been shown to have a fast acting and long lasting hypotensive effect. Human adrenomedullin consists of 52 amino acids, and is a member of the calcitonin gene related protein superfamily.³ It is present in high concentrations in the right atrium of the heart, where it reaches a 5 to 50-fold excess over the concentrations found in the left atrium and the ventricles, respectively, and also in several organs. In intact anaesthetised rats, a 1 nmol/kg dose of human adrenomedullin administered intravenously over 15 seconds resulted in an average fall in mean arterial pressure of 40 mm Hg.⁴

Clinical studies have implied that adrenomedullin operates through a NO dependent mechanism in producing potent and long lasting vasodilatory effects on skeletal muscle arteries. Plasma adrenomedullin concentrations have been shown to correlate with pulmonary capillary wedge pressure, pulmonary arterial pressure, right atrial pressure, and heart rate in the early stages of acute myocardial infarction.⁵ Recently, it has been shown that adrenomedullin concentrations are increased in patients undergoing percutaneous transluminal coronary angioplasty.⁶ In rats, adrenomedullin improved myocardial performance by increasing cardiac index and stroke volume with no effects on heart rate. This direct positive inotropic effect may work via the intracellular signalling molecule cyclic adenosine monophosphate (cAMP) to enhance myocardial contractility.⁷

Adrenomedullin plays an important role in cardiovascular regulation through its endocrine or paracrine action on other hormones. Hormones that are directly inhibited in synthesis and secretion by adrenomedullin include atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), since they also have hypotensive properties similar to adrenomedullin. Adrenomedullin has a diuretic effect that helps to control fluid and electrolyte balance and influences the secretion of adrenocorticotrophic hormone, aldosterone, and angiotensin.⁸

It has also been shown that adrenomedullin is synthesised and secreted by smooth muscle and endothelial cells into the circulation in response to various stimuli including hypoxia, endothelial dysfunction, and cardiopulmonary

bypass surgery.^{9, 10} The severity and the irreversibility of pulmonary hypertension has led several investigators to study the pathophysiology of this disease and to attempt using various vasoactive mediators for the treatment of pulmonary hypertension in humans.

Answers to pulmonary hypertension?

Several studies involving the infusion of adrenomedullin for the treatment of disease have been published. In heart failure patients, infusion of adrenomedullin showed higher potency haemodynamically compared to ANP and BNP in decreasing cardiac output and increasing cardiac output.^{11–13} Acute and chronic administrations of adrenomedullin have shown different responses in the development of pulmonary hypertension. Acute treatment of adrenomedullin did not slow the progression of the disease, whereas chronic administration of adrenomedullin in monocrotaline induced pulmonary hypertensive rats showed an attenuated development of the disease.¹⁴

In this issue of the journal, Nagaya and colleagues present the results of their study on the haemodynamics and hormonal effects of short term infusion of adrenomedullin in patients with precapillary pulmonary hypertension.¹⁵ Adrenomedullin was infused intravenously at a rate of 0.05 µg/kg/min for 30 minutes in seven patients with pulmonary hypertension. The placebo group comprised six patients who received saline. They measured systemic and pulmonary arterial blood pressures along with cardiac output and oxygen consumption. Upon adrenomedullin infusion, both cardiac index and heart rate increased. Pulmonary and systemic vascular resistance decreased about 35%. Pulmonary arterial oxygen saturation also increased. The haemodynamic results obtained were consistent with left heart failure. When they analysed blood adrenomedullin, BNP, cAMP, and aldosterone concentrations, all had increased in both the adrenomedullin and placebo groups. The concentrations of plasma adrenomedullin had increased by three times and cAMP by 23% by the end of the adrenomedullin infusion period. In patients infused with adrenomedullin the concentrations of aldosterone decreased and renin remained unchanged. The authors concluded that intravenous infusion of adrenomedullin has beneficial haemodynamic and hormonal effects in patients with precapillary pulmonary hypertension.

Uniqueness of the study

This study by Nagaya and colleagues is the first of its kind to investigate the therapeutic use of adrenomedullin in the treatment of pulmonary hypertension.¹⁵ Even though it involved only 13 patients, the study was a well designed, placebo controlled, randomised trial with the use of a low and physiologically tolerable dose. Only one patient experienced transient systemic hypotension. The transient decline seen in the systemic blood pressure is expected. A number of factors responsible for blood pressure control were measured. The interesting aspects are an increase in cardiac index, an increase in pulmonary oxygen saturation, and a decline in pulmonary vascular resistance. The unchanged concentrations of renin and noradrenaline (norepinephrine) were different from other published reports suggesting that intravenous administration of adrenomedullin greatly decreased plasma renin and

noradrenaline concentrations.^{16, 17} The authors should have addressed this difference in their discussion. It would also have been useful to see follow up data from these patients beyond the infusion period. Their results, however, clearly show that adrenomedullin has the potential to reduce the risks involved in pulmonary hypertension.

Heart and renal failure, myocardial infarction, congenital heart diseases, and chronic obstructive pulmonary disease predispose patients to elevated pulmonary artery pressures, resulting in pulmonary hypertension with impaired concentrations of vasoactive mediators. When these patients require surgical intervention, high postoperative pulmonary resistance can lead to right heart strain and failure. Medical treatment to reduce afterload in the pulmonary circulation remains unsatisfactory, since the systemic circulation is frequently more profoundly affected by vasodilator treatments than the pulmonary circulation. Prolonged intensive care unit stays and adverse effects on other organ systems can result from significant postoperative right heart failure.

The results from Nagaya's study highlights the applicability of a vasodilator, adrenomedullin, in the treatment of pulmonary hypertension, and in circumstances where control of the vascular tone is difficult to achieve, as in pulmonary hypertension seen after coronary artery bypass surgery. There is a need for such an agent, in addition to the ones currently used—NO and prostacyclin. Administration of NO and prostacyclin for the treatment of pulmonary hypertension has shown a rebound effect upon withdrawal. Being a peptide acting via cAMP (as shown by this study), and by decreasing aldosterone, adrenomedullin can modulate its vasodilatory activity on vascular endothelial and smooth muscle cells at the cellular level. This may inhibit the recurrence of pulmonary hypertension upon withdrawal of agents. Within 10 years, results from similar and long term studies with adrenomedullin may eventually help to develop strategies targeted at its use for the prevention and treatment of hypertensive disorders.

PALANISWAMY VIJAY

Department of Surgery,
Indiana University School of Medicine,
Indianapolis, IN 46202, USA
pvijay@iupui.edu

- 1 Bando K, Vijay P, Morelock RJ, *et al.* The perioperative dynamic changes of plasma endothelin-1 and nitric oxide in patients with pulmonary hypertension and congenital heart disease. *Circulation* 1996;**94**:2817.
- 2 Kitamura K, Kangawa K, Kawamoto M, *et al.* Adrenomedullin: a novel hypotensive peptide isolated from human pheochromocytoma. *Biochem Biophys Res Commun* 1993;**192**:553–6.
- 3 Kuwasako K, Kitamura K, Ichiki Y, *et al.* Human adrenomedullin N-terminal 20 peptide in pheochromocytoma and normal adrenal medulla. *Biochem Biophys Res Commun* 1995;**211**:694–699.
- 4 Ishiyama Y, Kitamura K, Ichiki Y, *et al.* Hemodynamic effects of a novel hypotensive peptide, human adrenomedullin, in rats. *Eur J Pharmacol* 1993;**241**:271–3.
- 5 Yoshitomi Y, Nishikimi T, Kojima S, *et al.* Plasma levels of adrenomedullin in patients with acute myocardial infarction. *Clin Sci* 1998;**94**:135–9.
- 6 Etoh T, Doi H, Hanada Y, *et al.* Cardiac secretion of adrenomedullin by percutaneous transluminal coronary angioplasty. *Horm Metab Res* 1997;**29**:530–1.
- 7 Szokodi I, Kinnunen P, Ruskoaho H. Inotropic effect of adrenomedullin in the isolated perfused rat heart. *Acta Physiol Scand* 1996;**156**:151–2.
- 8 Vesely DL, Blankenship M, Douglass MA, *et al.* Atrial natriuretic peptide increases adrenomedullin in the circulation of healthy humans. *Life Sci* 1996;**59**:243–54.
- 9 Ma L-N, Zhao S-P, Gao M, *et al.* Endothelial dysfunction associated with left ventricular diastolic dysfunction in patients with coronary heart disease. *Int J Cardiol* 2000;**72**:275–7.
- 10 Jougasaki M, Burnett JC. Adrenomedullin: potential in physiology and pathophysiology. *Life Sci* 2000;**66**:855–72.
- 11 Lainchbury JG, Troughton RW, Lewis LK, *et al.* Hemodynamic, hormonal, and renal effects of short-term adrenomedullin infusion in healthy volunteers. *Clin Endocrinol Metab* 2000;**85**:1016–20.
- 12 Lainchbury JG, Nicholls MG, Espiener EA, *et al.* Bioactivity and interactions of adrenomedullin and brain natriuretic peptide in patients with heart failure. *Hypertension* 1999;**34**:70–5.
- 13 Oya H, Nagaya N, Furuichi S, *et al.* Comparison of intravenous adrenomedullin with atrial natriuretic peptide in patients with congestive heart failure. *Am J Cardiol* 2000;**86**:94–8.
- 14 Vijay P, Sharp, Brown JW. Adrenomedullin and pulmonary hypertension. *Circulation* 1999;**100**:2908.
- 15 Nagaya N, Nishikimi T, Uematsu M, *et al.* Haemodynamic and hormonal effects of adrenomedullin in patients with pulmonary hypertension. *Heart* 2000;**84**:653–8.
- 16 Parkes DG, May CN. ACTH-suppressive and vasodilator actions of adrenomedullin in conscious sheep. *J Neuroendocrinol* 1995;**7**:923–9.
- 17 Fukuhara M, Tsuchihashi T, Abe I, *et al.* Cardiovascular and neurohormonal effects of intravenous adrenomedullin in conscious rabbits. *Am J Physiol* 1995;**269**:R1289–93.

STAMPS IN CARDIOLOGY

Congresses



The 7th World Pacing Symposium was held in Vienna 1-5th May 1983. The 4 schilling Austrian stamp was issued to mark this event and is one of the few stamps ever issued involving a pacemaker theme. The ECG is more in the form of a square wave depicting the pacemaker output voltage over a stylised heart.

M K DAVIES
A HOLLMAN